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PROCESS FOR THE PREPARATION OF N-(3-HYDROXY-SUCCINYL)-AMINO ACID DERIVATIVES

Abstract:

Abstract of WO 9843946

(A1) Processes for preparing compounds of the formula (I) are described: $P^{(1)}-OOC-CH(OH)-CHR^{(1)}-CONH-Z$ wherein $P^{(1)}$ is hydrogen or a protecting group, Z is a group $-CHR^{(2)}COOP^{(2)}$ or $-CHR^{(2)}CONR^{(3)}R^{(4)}$; wherein $P^{(2)}$ is hydrogen or a protecting group and $R^{(1)}$, $R^{(4)}$ are values known in the TNF-inhibitor art. The compounds of the formula (I) are useful in inhibiting TNF and one or more matrix metalloproteinase enzymes. One intermediate in a process of the invention is formula (II).

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(57) Abstract			
Processes for preparing compounds of the formula (I) are described: P ¹ OOC-CH(OH)-CHR ¹ -CONH-Z wherein P ¹ is hydrogen or a protecting group, Z is a group -CHR ² COOP ² or -CHR ² CONR ³ R ⁴ wherein P ² is hydrogen or a protecting group and R ¹ -R ⁴ are values known in the TNF-inhibitor art. The compounds of the formula (I) are useful in inhibiting TNF and one or more matrix metalloproteinase enzymes. One intermediate in a process of the invention is formula (II).			

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PROCESS FOR THE PREPARATION OF N-(3-HYDROXY-SUCCINYL)-AMINO ACID DERIVATIVES

This invention relates to a chemical process and to chemical intermediates useful in such a process.

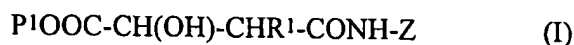
- 5 The chemical process of this invention is useful for preparing compounds which are inhibitors of the production of TNF (Tumour Necrosis Factor) which is believed to be formed by the cleavage of a pro-form, or larger precursor, by the enzyme pro-TNF Convertase. The chemical process of this invention is also useful for preparing compounds which are intermediates in the production of compounds which are inhibitors of the production of TNF.
- 10 Compounds which are inhibitors of the production of TNF will be useful in the treatment of disease or medical conditions in which excessive TNF production is known to give rise via a cascade of processes to a variety of physiological sequelae including the production of physiologically-active eicosanoids such as the prostaglandins and leukotrienes, the stimulation of the release of proteolytic enzymes such as collagenase, the activation of
- 15 osteoclast activity leading to the resorption of calcium, the stimulation of the release of proteoglycans from, for example, cartilage, the stimulation of cell proliferations and to angiogenesis. It is also known that, in certain cellular systems, TNF production precedes and mediates the production of other cytokines such as interleukin-1 (IL-1) and interleukin-2 (IL-2) which are also believed to contribute to the pathology of disease states such as
- 20 inflammatory and allergic diseases and cytokine-induced toxicity. Excessive TNF production has also been implicated in mediating or exacerbating the development of various inflammatory and allergic diseases such as inflammation of the joints (especially rheumatoid arthritis, osteoarthritis and gout), inflammation of the gastrointestinal tract (especially inflammatory bowel disease, ulcerative colitis and gastritis), skin disease (especially psoriasis,
- 25 eczema and dermatitis) and respiratory disease (especially asthma, bronchitis and allergic rhinitis), and in the production and development of various cardiovascular disorders such as myocardial infarction, angina and peripheral vascular disease. Excessive TNF production has also been implicated in mediating complications of bacterial, fungal and/or viral infections such as endotoxic shock, septic shock and toxic shock syndrome. Excessive TNF production
- 30 has also been implicated in mediating or exacerbating the development of adult respiratory distress syndrome, diseases involving cartilage or muscle resorption, Paget's disease and

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osteoporosis, pulmonary fibrosis, cirrhosis, renal fibrosis, the cachexia found in certain chronic diseases such as malignant disease and acquired immune deficiency syndrome (AIDS), tumour invasiveness and tumour metastasis and multiple sclerosis.

The compounds able to be prepared by the process of this invention may also be
 5 inhibitors of one or more matrix metalloproteinases such as collagenases, stromelysins and gelatinases. Thus they may also be of use in the therapeutic treatment of disease conditions mediated by such enzymes for example arthritis (rheumatoid and osteoarthritis), osteoporosis and tumour metastasis.

The present invention relates, more specifically, to a process for preparing compounds
 10 of the formula (I):



wherein P^1 is hydrogen, a salt forming cation or a protecting group, Z is a group
 15 $-CHR^2COOP^2$ or $-CHR^2CONR^3R^4$ wherein P^2 is hydrogen or a protecting group and R^1-R^4 are values known in this structural type of TNF inhibitor.

The compounds of the formula (I), when Z is $-CHR^2CONR^3R^4$ and P^1 is hydrogen or a salt-forming cation are active TNF inhibitors.

The compounds of the formula (I) wherein P^1 is hydrogen or a salt-forming cation
 20 may also be converted to the corresponding hydroxamic acid of the formula (II):



wherein R^1 and Z are as hereinbefore defined.

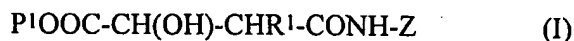
25 Compounds of the formulae (II) wherein Z is $-CHR^2CONR^3R^4$ are known TNF inhibitors. Compounds of the formula (II) wherein Z is $-CHR^2COOP^2$ may be converted to compounds of the formula (II) wherein Z is $-CHR^2CONR^3R^4$ by standard methods.

Compounds of the formulae (I) and/or (II), wherein Z is $-CHR^2CONR^3R^4$ are disclosed as TNF inhibitors for example in: WO 9633165, WO 9616931, WO 9606074,
 30 WO 9532944, WO 9519961, WO 9519957, WO 9519956, WO 9424140, WO 9402447, WO 9402446, WO 9533709, EPA 497192, EPA 236872, WO 9633176, WO 9633968,

WO 9506031 and WO 9522966.

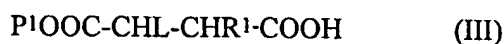
Accordingly the present invention provides a process for preparing a compound of the formula (I) or a salt thereof:

5



wherein P^1 is hydrogen or a protecting group;

Z is a group $-CHR^2COOP^2$ or $-CHR^2CONR^3R^4$ wherein P^2 is hydrogen or a protecting group
10 and R^1-R^4 are values known in the afore-mentioned disclosures, which process comprises reacting a compound of the formula (III):



15 wherein L is a leaving group, with a compound of the formula (IV):



and thereafter if necessary:

- 20 i) removing any protecting groups,
ii) forming a salt.

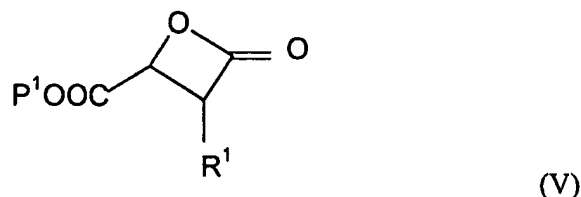
L is a leaving group. Suitably L is a leaving group such as halo, for example chloro, bromo or iodo, or a sulphonyloxy group, such as C_{1-6} alkanesulphonyloxy for example methanesulphonyloxy, benzenesulphonyloxy or 4-methylbenzenesulphonyloxy.

- 25 The reaction between the compounds of the formulae (III) and (IV) is conveniently performed at a non-extreme temperature for example -25°C to $+50^\circ\text{C}$ and more conveniently 0°C to $+30^\circ\text{C}$ and most conveniently at ambient temperature.

The reaction is typically performed in a substantially inert organic solvent for example an aprotic solvent such as acetonitrile or diethyl ether.

- 30 The reaction of the compounds of the formulae (III) and (IV) is believed to proceed via the formation of the lactone of the formula (V).

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wherein P¹ and R¹ are as hereinbefore defined.

5 The compound of the formula (IV) acts as a base which is believed to convert the carboxylic acid function of the compound of the formula (III) to a carboxylate anion and which then displaces the leaving group L to form the lactone. The lactone is believed to be ring-opened by nucleophilic attack of the compound of the formula (IV) to form the compound of the formula (I).

10 Therefore another aspect of the present invention provides a process for preparing a compound of the formula (I) or salt thereof as hereinbefore defined which comprises reacting a lactone of the formula (V) with a compound of the formula (IV) and thereafter, if necessary, removing any protecting groups and/or forming a salt.

15 The reaction between the compounds of the formulae (IV) and (V) takes place under conditions analogous to those for the reaction of compounds of the formulae (III) and (IV).

20 In another aspect the present invention provides a process for preparing a compound of the formula (V) as hereinbefore defined which comprises reacting a compound of the formula (III) with a non-nucleophilic base. In this way the base converts the carboxylic acid function of the compound of the formula (III) to a carboxylate anion which displaces L to form the lactone. However the non-nucleophilic base does not substantially react further with the lactone which may be isolated.

Suitable non-nucleophilic bases include both organic and inorganic bases.

25 Preferably the base is an inorganic base such as an alkali metal or alkaline earth metal carbonate or bicarbonate for example sodium bicarbonate, potassium carbonate, sodium carbonate or potassium bicarbonate. Suitably the reaction is performed under biphasic conditions with the compound of the formula (III) dissolved in an aprotic organic solvent such as acetonitrile, diethyl ether or dichloromethane which is stirred, typically vigorously, with an aqueous solution of the base at a non-extreme temperature for example at ambient

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temperature. The reaction may be monitored by thin layer chromatography or any other convenient methodology and, after a suitable period of time, the organic phase may be separated and worked-up to provide the compound of the formula (V). In an alternative the reaction is performed in the presence of a phase transfer catalyst for example benzyl

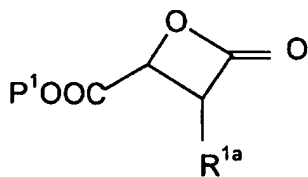
5 trimethylammonium chloride, again with stirring at a non-extreme temperature.

In an alternative the non-nucleophilic base, for reacting with a compound of the formula (III), may be an organic base for example a tertiary amine such as di-isopropylethylamine. The reaction of a non-nucleophilic organic base with a compound of the formula (III) is typically performed under conditions analogous to those for the reaction of
10 compound of the formulae (III) and (IV).

The present invention provides flexibility. In an advantageous aspect, it provides a "one-pot" reaction for preparing a compound of the formula (I) from the compounds of the formulae (III) and (IV). In another aspect, it can provide the compound of the formula (V) as a useful intermediate which can be reacted with a variety of compounds of the formula (IV).

15 The compounds of the formula (V) form another aspect of this invention.

Certain compounds of the formula (V) have been disclosed in the literature, in particular in the literature relating to polymers. Accordingly, the present invention provides a compound of the formula (VI):



(VI)

20 wherein P¹ is hydrogen or a protecting group and R^{1a} is a group R¹ as defined herein except that when P¹ is hydrogen, n-butyl, isopropyl, ethyl or allyl (-CH₂CH=CH₂), R^{1a} is not hydrogen and when P¹ is benzyl, R^{1a} is not hydrogen, methyl or isopropyl. In a particular
25 aspect R^{1a} is not hydrogen.

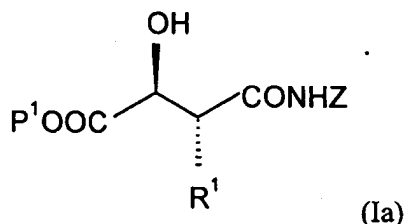
Preferably, in the compounds of the formula (VI), P¹ is benzyl or C₁₋₆alkyl, for example methyl, ethyl, n-propyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl.

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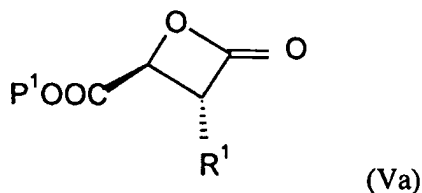
Preferred values of R^{1a} in the compounds of the formula (VI) are as described herein in relation to R^1 in the compounds of the formula (I).

Particular compounds of this invention include 3R-isobutyl-4-oxo-2S-oxetane carboxylic acid tert butyl ester and 3R-(4-benzyloxybutyl)-4-oxo-2S-oxetane carboxylic acid tert butyl ester.

In a preferred aspect, the process of the present invention provides compounds of the formula (Ia):



10 wherein P^1 , R^1 and Z are as hereinbefore defined, from compounds of the formulae (III) and (IV). The reaction is believed to proceed via the formation of the lactone of the formula (Va):



15 wherein P^1 and R^1 are as hereinbefore defined. Preferred and particular values for P^1 , R^1 and Z in the compounds of the formulae (Ia) and (Va) are as described for the compounds of the formulae (I) and (V) respectively. Thus in a further aspect the present invention provides the compounds of the formula (Va) wherein R^1 is R^{1a} and P^1 and R^{1a} are as defined as in relation to formula (VI) hereinabove.

20 The compounds of the formula (III) form another aspect of this invention. Certain compounds of the formula (III) have been disclosed in the literature.

Accordingly the present invention provides a compound of the formula (VII):



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wherein P¹ is hydrogen or a protecting group, R¹ is as herein defined and L¹ is a sulphonyloxy group or halo except that:

- i) when P¹ is hydrogen and R¹ is methyl or ethyl, L¹ is not bromo;
- ii) when P¹ is hydrogen and R¹ is methyl, L¹ is not chloro;
- 5 iii) when P¹ is isopropyl and R¹ is methyl, L¹ is not chloro or iodo.

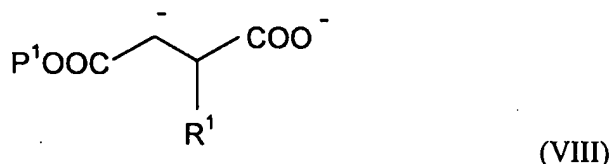
Preferably in the compounds of the formula (VII), P¹ is benzyl or C₁₋₆alkyl for example methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or tert-butyl.

Preferably L¹ is bromo, chloro or iodo.

Preferred values of R¹ in the compounds of the formula (VII) are as described herein
10 in relation to R¹ in the compounds of the formula (I).

Particular compounds of this invention include 3R-chloro-2S-isobutylbutan-1,4-dioic acid 4-tert-butyl ester and 3R-chloro-2S-(4-benzyloxybutyl)butan-1,4-dioic acid 4-tert-butyl ester.

The compounds of the formula (III) may be prepared by reacting a dianion of the
15 formula (VIII):



wherein P¹ and R¹ are as hereinbefore defined, with a source of the group L.

Suitable sources of halo include carbon tetrachloride and carbon tetrabromide.

- 20 Typically the dianion of the formula (VIII) is formed by reacting the corresponding neutral compound with a non-nucleophilic base, for example lithium di-isopropylamide at low temperatures (-78°C) to form the dianion which is then reacted with the source of the group L.

The neutral compounds corresponding to the formula (VIII) are known in, or may be made by, the methods of the literature.

- 25 As stated hereinbefore the reaction of the compounds of the formulae (III) and (IV), or the reaction of the compounds of the formulae (IV) and (V), provides the compounds of the formula (I) or a salt thereof. The compounds of the formula (I) are optionally protected on the carboxylic acid function with a protecting group P¹.

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The protecting group P¹ may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the carboxyl group, and may be introduced by conventional methods.

Protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

Specific examples of protecting groups are given below for the sake of convenience, in which "lower" signifies that the group to which it is applied preferably has 1-4 carbon atoms. It will be understood that these examples are not exhaustive. Where specific examples of methods for the removal of protecting groups are given below these are similarly not exhaustive. The use of protecting groups and methods of deprotection not specifically mentioned is of course within the scope of the invention.

A carboxyl protecting group may be the residue of an ester-forming aliphatic or araliphatic alcohol or of an ester-forming silanol (the said alcohol or silanol preferably containing 1-20 carbon atoms).

Examples of carboxy protecting groups include straight or branched chain (1-12C)alkyl groups (eg isopropyl, t-butyl); lower alkoxy lower alkyl groups (eg methoxymethyl, ethoxymethyl, isobutoxymethyl); lower aliphatic acyloxy lower alkyl groups, (eg acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl); lower alkoxycarbonyloxy lower alkyl groups (eg 1-methoxycarbonyloxyethyl, 1-ethoxycarbonyloxyethyl); aryl lower alkyl groups (eg benzyl, p-methoxybenzyl, o-nitrobenzyl, p-nitrobenzyl, benzhydryl and phthalidyl); tri(lower alkyl)silyl groups (eg trimethylsilyl and t-butyldimethylsilyl); tri(lower alkyl)silyl lower alkyl groups (eg trimethylsilylethyl); and (2-6C)alkenyl groups (eg allyl and vinyl ethyl).

Methods particularly appropriate for the removal of carboxyl protecting groups include for example acid-, base-, metal- or enzymically-catalysed hydrolysis.

Any other functional group in the compounds of the formulae (III)-(V) may be protected as necessary. Such protecting groups may in general be chosen from any of the groups described in the literature or known to the skilled chemist as appropriate for the protection of the group in question, and may be introduced by conventional methods. Such

protecting groups may be removed by any convenient method as described in the literature or known to the skilled chemist as appropriate for the removal of the protecting group in question, such methods being chosen so as to effect removal of the protecting group with minimum disturbance of groups elsewhere in the molecule.

5 Examples of hydroxyl protecting groups include lower alkyl groups (eg *t*-butyl), lower alkenyl groups (eg allyl); lower alkanoyl groups (eg acetyl); lower alkoxy carbonyl groups (eg *t*-butoxycarbonyl); lower alkenyloxycarbonyl groups (eg allyloxycarbonyl); aryl lower alkoxy carbonyl groups (eg benzoyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl);
10 tri lower alkylsilyl (eg trimethylsilyl, *t*-butyldimethylsilyl) and aryl lower alkyl (eg benzyl) groups.

 Examples of amino protecting groups include formyl, aralkyl groups (eg benzyl and substituted benzyl, *p*-methoxybenzyl, nitrobenzyl and 2,4-dimethoxybenzyl, and triphenylmethyl); di-*p*-anisylmethyl and furylmethyl groups; lower alkoxy carbonyl (eg
15 *t*-butoxycarbonyl); lower alkenyloxycarbonyl (eg allyloxycarbonyl); aryl lower alkoxy carbonyl groups (eg benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *o*-nitrobenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl); trialkylsilyl (eg trimethylsilyl and *t*-butyldimethylsilyl); alkylidene (eg methylenidene); benzylenidene and substituted benzylenidene groups.

20 Methods appropriate for removal of hydroxy and amino protecting groups include, for example, acid-, base-, metal- or enzymically-catalysed hydrolysis, for groups such as *p*-nitrobenzyloxycarbonyl, hydrogenation and for groups such as *o*-nitrobenzyloxycarbonyl, photolytically.

 The compounds of the formula (I) wherein P¹ is hydrogen or an activated derivative
25 thereof, optionally wherein the hydroxy group in -CH(OH)- is protected, may be reacted with hydroxylamine, O-protected hydroxylamine or a salt thereof (followed by deprotection as necessary) to provide the hydroxamic acid compounds of the formula (II) as hereinbefore described.

 The compound of the formula (I) may be reacted in the form of the acid or an
30 activated derivative thereof such as an acid halide, acid anhydride or an 'activated' ester such as 1H-benzo[1,2,3]triazol-1-yl, 1-hydroxy-benzo[1,2,3]triazole, pentafluorophenyl or 2,4,5-

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trichlorophenyl. The reaction of the compound of the formula (I) and hydroxylamine is performed under standard conditions. Typically the reaction of an activated ester of a compound of the formula (I) and hydroxylamine or O-protected hydroxylamine (for example protected with benzyl, t-butyl or silyl) is performed in the presence of a base, for example 2,6-lutidine in an anhydrous aprotic solvent, for example dimethylformamide, at a non-extreme temperature, for example in the region -30° to $+25^{\circ}$, preferably about 0°C .

The processes of this invention may provide the compounds of the formula (I) in the form of a salt. In one aspect the compound is in the form of a pharmaceutically acceptable salt. Suitable pharmaceutically acceptable salts include acid addition salts such as hydrochloride, hydrobromide, citrate and maleate salts and salts formed with phosphoric and sulphuric acid. In another aspect suitable salts are base salts such as an alkali metal salt for example sodium or potassium, an alkaline earth metal salt for example calcium or magnesium, or organic amine salt for example triethylamine. In another aspect the compound is in the form of a non-pharmaceutically acceptable salt which may be a useful intermediate in preparing pharmaceutically acceptable salts of either of the compounds of the formula (I) or (II).

In the compounds of the formula (I), Z may be $-\text{CHR}^2\text{COOP}^2$ wherein P^2 is hydrogen or a protecting group. Such compounds may be deprotected (P^2 is hydrogen) and reacted with a compound of the formula (IX):

20



wherein R^3 and R^4 are as herein defined under standard peptide coupling conditions.

Alternatively a corresponding compound of the formula (II) may be deprotected (P^2 is hydrogen) and reacted with a compound of the formula (IX) under standard peptide coupling conditions.

Thus in another aspect the present invention provides a process for preparing compounds of the formula (II) which comprises reacting compounds of the formulae (III) and (IV) (or compounds of the formulae (IV) and (V)) and, subsequently reacting the product with hydroxylamine, O-protected hydroxylamine or a salt thereof.

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The compounds of the formulae (I) and (II) may be formulated and tested according to the methods of the literature.

In the compounds of the formulae (I) and (II), R¹-R⁴ may have any value known for this structure in the TNF-inhibition literature and, in particular, known in the list of
5 disclosures provided hereinbefore.

More particularly:

- R¹ is alkyl; alkenyl; alkynyl; phenylalkyl; heteroarylalkyl; cycloalkylalkyl;
 cycloalkenylalkyl; phenylalkoxyalkyl; heteroarylalkoxyalkyl;
- 10 C₁₃₋₂₄ hydrocarbon chain optionally interrupted by one or more non-adjacent
 nitrogen, oxygen, sulphur, CO, SO, SO₂ groups;
- R² is the characterising group of a non-natural α -amino acid in which any functional
 groups may be protected;
- 15 the side chain of a naturally occurring amino acid in which any functional groups
 may be protected;
- 20 CR^xR^yR^z wherein each of R^x, R^y, R^z is independently hydrogen, alkyl, alkenyl,
 alkynyl, phenylalkyl, halo, cyano, carboxy, alkoxycarbonyl, phenyl, heteroaryl, or R^x
 and R^y together with the carbon atom to which they are linked form a cycloalkyl or
 heterocyclic ring, or R^x, R^y and R^z together with the carbon atom to which they are
 linked form a bicyclic ring for example adamantyl;
- 25 phenyl, pyridyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, pyrazolyl, thiopyrazolyl,
 isoxazolinyl, benzimidazolyl, benzoxazolyl or benzthiazolyl, any of which is
 optionally substituted;
- 30 R³ is CHR^aR^b wherein R^a and R^b independently represent phenyl or heteroaryl, which
 rings may be optionally linked by a bond or a C₁₋₄ alkylene or C₂₋₄alkenylene bridge,
 either of which may be interrupted by oxygen or sulphur;

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-(Z-O)_n-Z wherein Z is C₁₋₆alkyl optionally interrupted by one or more non-adjacent sulphur or nitrogen atoms, n is >1;

- 5 C₃₋₈cycloalkyl or C₄₋₈cycloalkenyl; perfluoro C₁₋₄alkyl; alkyl; hydrogen; phenylalkyl; phenyl; heteroaryl; naphthyl;

R⁴ is hydrogen or alkyl.

- 10 Suitably alkyl (in "alkyl" and in any term containing "alkyl") is C₁₋₁₂alkyl, preferably C₁₋₆alkyl. Suitably alkenyl is C₂₋₁₂alkenyl, preferably C₂₋₆alkenyl. Suitably alkynyl is C₂₋₆alkynyl. Suitably cycloalkyl is C₃₋₈cycloalkyl.

- Any alkyl, cycloalkyl, cycloalkoxy, naphthyl, phenyl or heteroaryl ring is optionally substituted by one, two or three substituents selected from alkyl, alkoxy, alkylthio, phenoxy,
 15 phenylalkoxy, halo, cyano, carboxy, hydroxy, amino, alkylamino, dialkylamino, mercapto, alkylaminosulphonyl, dialkylaminosulphonyl, cyanoalkyl, aminoalkyl, alkanoylamino, alkoxycarbonylamino, alkanoyl, trifluoromethyl, alkanoylamino, aryl, phenyl, arylalkyl, aryloxy, arylalkoxy, heteroaryl, heteroarylalkyl, heterocyclyl, heterocyclylalkyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, hydroxyethyl, perfluoroC₁₋₄alkyl, alkylsulphiny, alkylsulphonyl, nitro, alkenyl, alkynyl, cycloalkyl, cycloalkenyl,
 20 benzyl, guanidine, pyrrolidino, morpholino or piperidino.

Favourably:

- R¹ is hydrogen, C₁₋₈alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₈cycloalkyl, aryl, heteroaryl, heterocyclyl, arylC₁₋₆alkyl, heteroarylC₁₋₆alkyl, heterocyclylC₁₋₆alkyl or
 25 C₃₋₈cycloalkylC₁₋₆alkyl;
 R² is C₁₋₆alkyl, C₂₋₆alkenyl, arylC₁₋₆alkyl, heteroarylC₁₋₆alkyl or the side-chain of a naturally occurring amino acid;
 R³ is hydrogen, C₁₋₆alkyl, C₃₋₈cycloalkyl, C₄₋₈cycloalkenyl, arylC₁₋₆alkyl, heteroarylC₁₋₆alkyl or heterocyclylC₁₋₆alkyl;
 30 R⁴ is hydrogen or C₁₋₆alkyl; or R³ or R⁴ together with the nitrogen atom to which they are joined form a heterocyclic ring;

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wherein any group or ring, in R^1 - R^4 , is optionally substituted, and wherein "aryl in the terms" "aryl" and "aryl C_{1-6} alkyl" typically means phenyl or naphthyl, preferably phenyl, and "heteroaryl" in the terms "heteroaryl" and "heteroaryl C_{1-6} alkyl" means an aromatic mono- or bicyclic 5-10 membered ring with up to five ring heteroatoms selected from nitrogen, oxygen and sulphur. (Examples of 'heteroaryl' include thienyl, pyrrolyl, furanyl, imidazolyl, thiazolyl, pyrimidinyl, pyridinyl, indolyl, benzimidazolyl, benzthiazolyl, quinolinyl and isoquinolinyl). "Heterocyclyl" in the term "heterocyclyl C_{1-6} alkyl" means a non-aromatic mono- or bicyclic 5-10 membered ring with up to five ring hetero atoms selected from nitrogen, oxygen and sulphur. (Examples of "heterocyclyl" include pyrrolidinyl, morpholinyl, piperidinyl, dihydropyridinyl and dihydropyrimidinyl).

Any group or ring in R^1 - R^4 may be optionally substituted, for example by up to three substituents which may be the same or different. Typical substituents include: hydroxy, C_{1-6} alkoxy for example methoxy, mercapto, C_{1-6} alkylthio for example methylthio, amino, C_{1-6} alkylamino for example methylamino, di- $(C_{1-6}$ alkyl)amino for example dimethylamino, carboxy, carbamoyl, C_{1-6} alkylcarbamoyl for example methylcarbamoyl, di- C_{1-6} alkylcarbamoyl for example dimethylcarbamoyl, C_{1-6} alkylsulphonyl for example methylsulphonyl, arylsulphonyl for example phenylsulphonyl, C_{1-6} alkylaminosulphonyl for example methylaminosulphonyl, di- $(C_{1-6}$ alkyl)aminosulphonyl for example dimethylamino-sulphonyl, nitro, cyano, cyano C_{1-6} alkyl for example cyanomethyl, hydroxy C_{1-6} alkyl for example hydroxymethyl, amino C_{1-6} alkyl for example aminoethyl, C_{1-6} alkanoylamino for example acetamido, C_{1-6} alkoxycarbonylamino for example methoxycarbonylamino, C_{1-6} alkanoyl for example acetyl, C_{1-6} alkanoyloxy for example acetoxy, C_{1-6} alkyl for example methyl, ethyl, isopropyl or tert-butyl, halo for example fluoro, chloro or bromo, trifluoromethyl, aryl for example phenyl, aryl C_{1-6} alkyl for example benzyl, aryloxy for example phenoxy, aryl C_{1-6} alkoxy for example benzyloxy, heteroaryl, heteroaryl C_{1-6} alkyl, heterocyclyl and heterocyclyl C_{1-6} alkyl. The term "side chain of a naturally occurring amino acid" means the side chain X of an amino acid NH_2 -CHX-COOH. Suitable amino acids include alanine, arginine, aspartic acid, cysteine, asparagine, glutamine, histidine, homoserine, isoleucine, leucine, lysine, methionine, norleucine, norvaline, ornithine, serine, threonine, tryptophan, tyrosine and valine.

The compounds of the formulae (I) and (II) possess a number of chiral centres, at the carbon atom adjacent to the HONHOC- group, at $-\text{CHR}^2-$, at $-\text{CHR}^1-$ (when R^1 is not hydrogen) and possibly in the variables R^1-R^4 . The processes of the present invention may be used to prepare diastereoisomers and mixtures thereof that inhibit TNF Convertase and/or

5 inhibit matrix metalloproteinase enzymes.

Favoured groups for R^1 include C_{1-8} alkyl for example isopropyl, n-propyl, isobutyl, sec-butyl, n-butyl, tert-butyl, isopentyl, n-pentyl, hexyl, heptyl or octyl; C_{1-8} alkyl interrupted by an oxygen or sulphur atom for example methoxypropyl, ethoxyethyl, propoxymethyl, ethylthioethyl or methylthiopropyl; phenyl C_{1-6} alkyl for example benzyl, phenethyl,

10 phenylpropyl or phenylbutyl; aryl C_{1-6} alkyl interrupted by oxygen or sulphur for example benzyloxybutyl or benzyloxypropyl; C_{3-8} cycloalkyl for example cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl; aryl C_{1-6} alkyl interrupted by oxygen or sulphur for example benzyloxybutyl or benzyloxypropyl; or C_{3-8} cycloalkyl C_{1-6} alkyl for example cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl or

15 cyclohexylmethyl.

Preferably R^1 is isobutyl.

There is a chiral centre at $-\text{CHR}^1-$ (when R^1 is not hydrogen); it is preferred that this centre has the configuration indicated in formula (X) hereinafter. For most values of R^1 this